SUBLINGUAL OR BUCCAL PHARMACEUTICAL COMPOSITION

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The invention relates to a sublingual or buccal pharmaceutical composition, and more specifically to a sublingual or buccal composition for the treatment of various mental disorders.

The compound trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole and the preparation thereof are disclosed in U.S. Pat. No. 4,145,434. The compound is described as having CNS-depressant activity and antihistamine and antiserotonin activities.

The pharmacological profile of trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, its kinetics and metabolism, as well as the first safety and efficacy studies in human volunteers and in schizophrenic patients were reviewed by De Boer et al. (Drugs of the Future 1993, 18(12), 1117–1123). It has been established that Org 5222 [5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1)] is a very potent dopamine and serotonin antagonist with potential antipsychotic activity.

Phase I clinical studies on the effects of perorally administered trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole however, revealed that serious cardiotoxic effects, e.g. postural hypotension and/or impairment of baroreceptor functioning, occurred.

Surprisingly, it has now been found that on sublingual or buccal administration, trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole has substantially less cardiovascular side effects.

The invention therefore relates to a sublingual or buccal pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino [4,5-c]pyrrole or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable auxiliaries suitable for use in sublingual or buccal compositions.

The compositions of the invention are useful in treating mammals, including humans, suffering from diseases which are susceptible to treatment by trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. Such diseases include mental disorders, such as tension, excitation, anxiety, psychosis, and schizophrenia. The compositions may also be used for antihistamine and for antiserotonin related diseases.

In its simplest form the pharmaceutical composition of the invention consists of an aqueous solution, for instance comprising 0.9% (w/v) of sodium chloride and the active compound 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, or a pharmaceutically acceptable salt thereof. The maleate salt (Org 5222) is a preferred salt. The active compound is rapidly absorbed from these aqueous pharmaceutical compositions, when kept under the tongue or in the mouth of a patient.

Preferred pharmaceutical compositions are solid pharmaceutical compositions which rapidly disintegrate in the mouth of a subject, upon insertion into the buccal pouch or upon placement under the tongue. Rapid disintegration means that the pharmaceutical composition is disintegrated within 30 seconds in water at 37° C., and preferably within 10 seconds, as measured according to the procedure described in Remington's Pharmaceutical Sciences, 18th Edition (Ed. A. R. Genaro), 1990, pp 1640–1641; see also US Pharmacopeia, Chapter <701>.

In a preferred embodiment the pharmaceutical compositions of the invention are tablets or lozenges which comprise a rapidly disintegrating composition of a pharmaceutically acceptable water-soluble or water-dispersable carrier material. Tablets and lozenges comprising a rapidly disintegrating composition of a pharmaceutically acceptable water-soluble or water-dispersable carrier material are known in the art, for example as disclosed in U.S. Pat. No. 4,371,516. Such tablets may be prepared by freeze-drying of an aqueous solution comprising 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, a water-soluble or water-dispersable carrier material and, optionally, pharmaceutically acceptable excipients. Such excipients are known in the art, see for instance Remington's Pharmaceutical Sciences, 18th Edition (Ed. A. R. Genaro), 1990, pp 1635–1638, and are commonly used in pharmaceutical compositions, for instance surfactants, colouring agents, flavouring agents, preservatives and the like.

The water-soluble or water-dispersable carrier material is preferably water-soluble. Suitable water-soluble carrier materials are (poly)saccharides like hydrolysed dextran, dextrin, mannitol, and alginates, or mixtures thereof, or mixtures thereof with other carrier materials like polyvinylalcohol, polyvinylpyrrolidine and water-soluble cellulose derivatives, like hydroxypropyl cellulose.

A preferred carrier material is gelatin, especially partially hydrolysed gelatin. The partially hydrolysed gelatin can be prepared by heating of a solution of gelatin in water, for example in an autoclave at about 120° C. for up to 2 hours. The hydrolysed gelatin is used in concentrations of about 1 to 6% (w/v), and preferably in concentrations of about 2 to 4% (w/v).

The preferred dosage forms of the composition of the invention, i.e. tablets or lozenges, can be prepared by methods known in the art. For example, according to a method as disclosed in British Patent 2,111,423, an aqueous composition comprising a predetermined amount of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino[4,5-c]pyrrole, a pharmaceutically acceptable water-soluble or water-dispersable carrier material and optionally pharmaceutically acceptable auxiliaries and excepients, is transferred into a mould, after which the composition is frozen and the solvent is sublimed, preferably by freeze-drying. The composition preferably contains a surfactant, for example Tween 80 (polyoxyethylene (20) sorbitan mono-oleate), which may help to prevent the freeze-dried product from sticking to the surface of the mould.

The mould may comprise a series of cylindrical or other shape depressions, each having a size corresponding to the desired size of the dosage form. Alternatively, the mould may have a larger size than the desired size of the dosage form, and after the contents are freeze-dried the product can be cut into the desired size. Preferably the dosage form is freeze-dried in the form of a lyosphere, which is a freeze-dried spherical-shaped droplet containing the active ingredient.

A preferred mould would correspond to a depression in a sheet of film material, as for example disclosed in U.S. Pat. No. 4,305,502 and U.S. Pat. No. 5,046,618. The film material may be similar to that employed in conventional blister packs.

Each dosage form of the pharmaceutical composition of the present invention comprises one dosage unit of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz-[2,3:6,7]oxepino[4,5-c]pyrrole as active ingredient. A dosage unit may contain between 0.005 mg and 15 mg of the active ingredient. Preferably the dosage unit contains 0.03–0.50 mg of 5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole.